RYBREVANT® (amivantamab-vmjw)
Injection for IV Use | 350 mg/7 mL (50 mg/mL)

+

LAZCLUZE™ (lazertinib)
Tablets | 240 mg/80 mg

Dosing and Administration Guide

For all RYBREVANT®-based regimens

INDICATIONS

RYBREVANT® (amivantamab-vmjw) is indicated:

- in combination with LAZCLUZE™ (lazertinib) for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations, as detected by an FDA-approved test.
- in combination with carboplatin and pemetrexed for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with an EGFR tyrosine kinase inhibitor.
- in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test.
- as a single agent for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

SELECT IMPORTANT SAFETY INFORMATION

Warnings and Precautions for RYBREVANT® and LAZCLUZE™ include infusion-related reactions, interstitial lung disease/pneumonitis, venous thromboembolic events, dermatologic adverse reactions, ocular toxicity, and embryo-fetal toxicity.

Please see full Important Safety Information. Please read full Prescribing Information for RYBREVANT® and full Prescribing Information for LAZCLUZE™.

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How RYBREVANT® works[1]

Amivantamab is a bispecific antibody that binds to the extracellular domains of EGFR and MET.[1]

In *in vitro* and *in vivo* studies, amivantamab was able to disrupt EGFR and MET signaling functions in mutation models of exon 19 deletions, exon 21 L858R substitutions, and exon 20 insertions through blocking ligand binding or degradation of EGFR and MET.[1]

The presence of EGFR and MET on the surface of tumor cells also allows for targeting of these cells for destruction by immune effector cells, such as natural killer cells and macrophages, through antibody-dependent cellular cytotoxicity and trogocytosis mechanisms, respectively.[1]

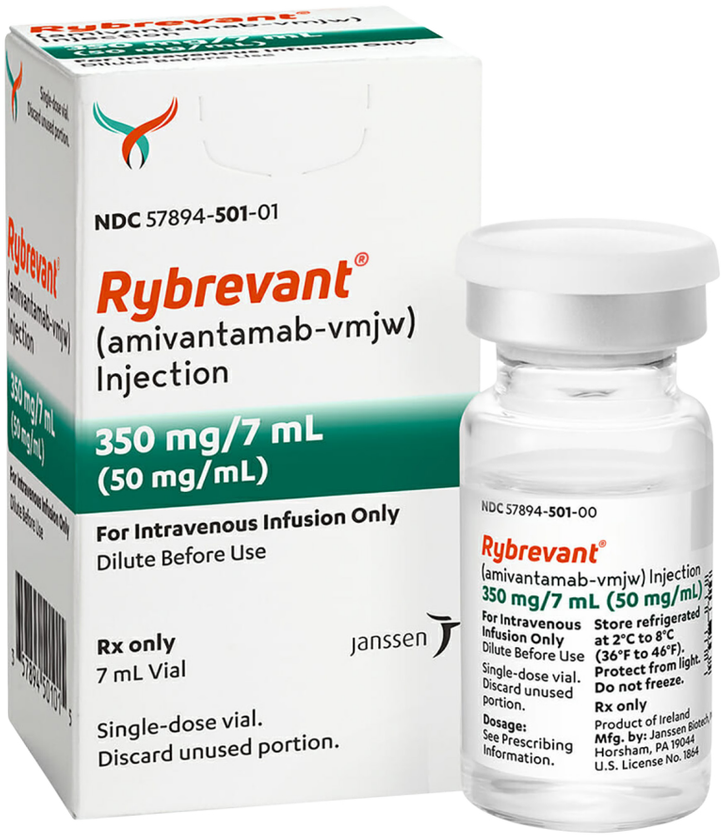
RYBREVANT® is an intravenous infusion indicated in combination with LAZCLUZE™, in combination with chemotherapy, or as a single agent.[1]

RYBREVANT® + LAZCLUZE™: LAZCLUZE™ is a third-generation TKI that is a suitable combination partner for RYBREVANT® because of its high selectivity for mutant EGFR, low selectivity for wild-type EGFR, and because it is CNS–penetrant.[2,3]

RYBREVANT® + LAZCLUZE™ is a chemotherapy-free combination that provides complementary extra- and intracellular antitumor activity and CNS penetration[1-4]

CNS, central nervous system; EGFR, epidermal growth factor receptor; MET, mesenchymal-epithelial transition; TKI, tyrosine kinase inhibitor.

RYBREVANT® storage and handling[1]



RYBREVANT® is a sterile, preservative-free, colorless to pale yellow solution for intravenous infusion.

- Each single-dose vial contains 350 mg/7 mL (50 mg/mL) of RYBREVANT®
- Each vial is individually packed in a single carton (NDC 57894-501-01)

Store vials in a refrigerator at 36 °F to 46 °F (2 °C to 8 °C) in the original carton to protect from light. Do not freeze

How to prepare RYBREVANT® before administration[1]

STEP 1

Check that the RYBREVANT® solution is colorless to pale yellow. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if discoloration or visible particles are present

STEP 2

Determine the dose and number of vials of RYBREVANT® needed based on patient's baseline weight

- Each vial of RYBREVANT® contains 350 mg of amivantamab-vmjw

STEP 3

Withdraw and then discard a volume of either 5% dextrose injection or 0.9% sodium chloride injection from the 250 mL infusion bag equal to the volume of RYBREVANT® to be added (ie, discard 7 mL diluent from the infusion bag for each RYBREVANT® vial)

- **Only use infusion bags** made of PVC, PP, PE, or PP+PE

STEP 4

Withdraw 7 mL of RYBREVANT® from each vial and add it to the infusion bag. The final volume in the infusion bag should be 250 mL

- **Discard** any unused portion left in the vial

STEP 5

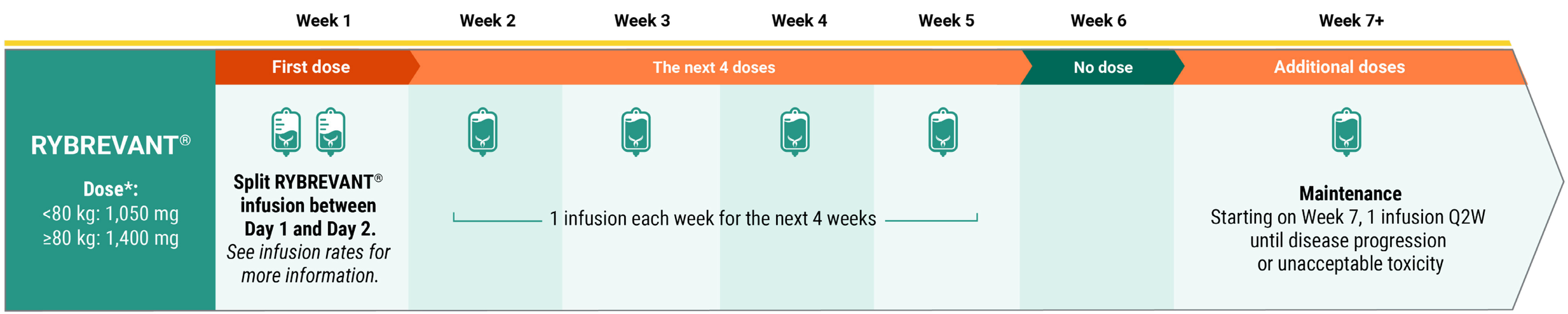
Gently invert the bag to mix the solution. Do not shake

STEP 6

Diluted solutions should be administered within 10 hours (including infusion time) at room temperature 59 °F to 77 °F (15 °C to 25 °C)

PE, polyethylene; PP, polypropylene; PVC, polyvinyl chloride.

Recommended dosing schedule for RYBREVANT® + LAZCLUZE™[1,2]



RYBREVANT®: The recommended dosage of RYBREVANT® is based on baseline body weight and administered as an intravenous infusion after dilution.

With LAZCLUZE™: When given in combination with LAZCLUZE™, administer RYBREVANT® any time after LAZCLUZE™ when given on the same day.

Refer to the full **Prescribing Information** for LAZCLUZE™ for recommended LAZCLUZE™ dosage and administration information.

When given in combination with LAZCLUZE™, administer RYBREVANT® any time after LAZCLUZE™ when given on the same day

*Dose adjustments not required for subsequent body weight changes.
Q2W, once every 2 weeks.

Please see full Important Safety Information. Please read full Prescribing Information for RYBREVANT® and full Prescribing Information for LAZCLUZE™.

RYBREVANT® + LAZCLUZE™ administration[1]

RYBREVANT®

- **Administer the diluted RYBREVANT® solution by intravenous infusion** using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding PES filter (pore size 0.2 micrometer)
- Administration sets must be made of PU, PBD, PVC, PP, or PE
- The administration set with filter must be primed with either 5% dextrose injection or 0.9% sodium chloride injection prior to the initiation of each RYBREVANT® infusion
- **Do not infuse RYBREVANT® concomitantly in the same intravenous line with other agents**

RYBREVANT® in combination with LAZCLUZE™

- Administer RYBREVANT® infusion every 2 weeks intravenously according to the infusion rates (see **infusion rates**)
- Administer RYBREVANT® via a peripheral line on Week 1 and Week 2, given the high incidence of IRRs during initial treatment
- RYBREVANT® may be administered via a central line for subsequent weeks
- **For the initial infusion**, prepare RYBREVANT® as close to administration time as possible to allow for the possibility of extended infusion time in the event of an infusion-related reaction
- Administer LAZCLUZE™ any time before RYBREVANT® when given on the same day

IRR, infusion-related reaction; PBD, polybutadiene; PE, polyethylene; PES, polyethersulfone; PP, polypropylene; PU, polyurethane; PVC, polyvinylchloride.

Please see full Important Safety Information. Please read full Prescribing Information for RYBREVANT® and full Prescribing Information for LAZCLUZE™.

RYBREVANT® + LAZCLUZE™ administration (cont'd)[2]

Dosing Information for LAZCLUZE™ when given in combination with RYBREVANT®

- **Swallow LAZCLUZE™ tablets whole (with or without food)**. Do not crush, split, or chew. Continue treatment until disease progression or unacceptable toxicity
- If a patient misses a dose of LAZCLUZE™ within 12 hours, instruct the patient to take the missed dose. If more than 12 hours have passed since the dose was to be given, instruct the patient to take the next dose at its scheduled time
- If vomiting occurs any time after taking LAZCLUZE™, instruct the patient to take the next dose at its next regularly scheduled time

Drug interactions with LAZCLUZE™

- Avoid concomitant use of LAZCLUZE™ with strong and moderate CYP3A4 inducers. Consider an alternate concomitant medication with no potential to induce CYP3A4
- Monitor for adverse reactions associated with a CYP3A4 or BCRP substrate where minimal concentration changes may lead to serious adverse reactions, as recommended in the approved product labeling for the CYP3A4 or BCRP substrate

Refer to the full **Prescribing Information** for LAZCLUZE™ for information regarding dosing and drug interactions.

BCRP, breast cancer resistance protein; CYP3A4, cytochrome P450 3A4.

Infusion rates for RYBREVANT® in combination with LAZCLUZE™[1]

Body Weight <80 kg			
Week	**Dose (per 250 mL bag)**	**Initial infusion rate**	**Subsequent infusion rate***
Week 1 (split dose infusion)			
Week 1, Day 1	350 mg	50 mL/hr	75 mL/hr
Week 1, Day 2	700 mg	50 mL/hr	75 mL/hr
Week 2	1,050 mg	85 mL/hr	
Week 3	1,050 mg	125 mL/hr	
Week 4	1,050 mg	125 mL/hr	
Week 5	1,050 mg	125 mL/hr	
Week 6	No dose		
Week 7, and every 2 weeks thereafter	1,050 mg	125 mL/hr	

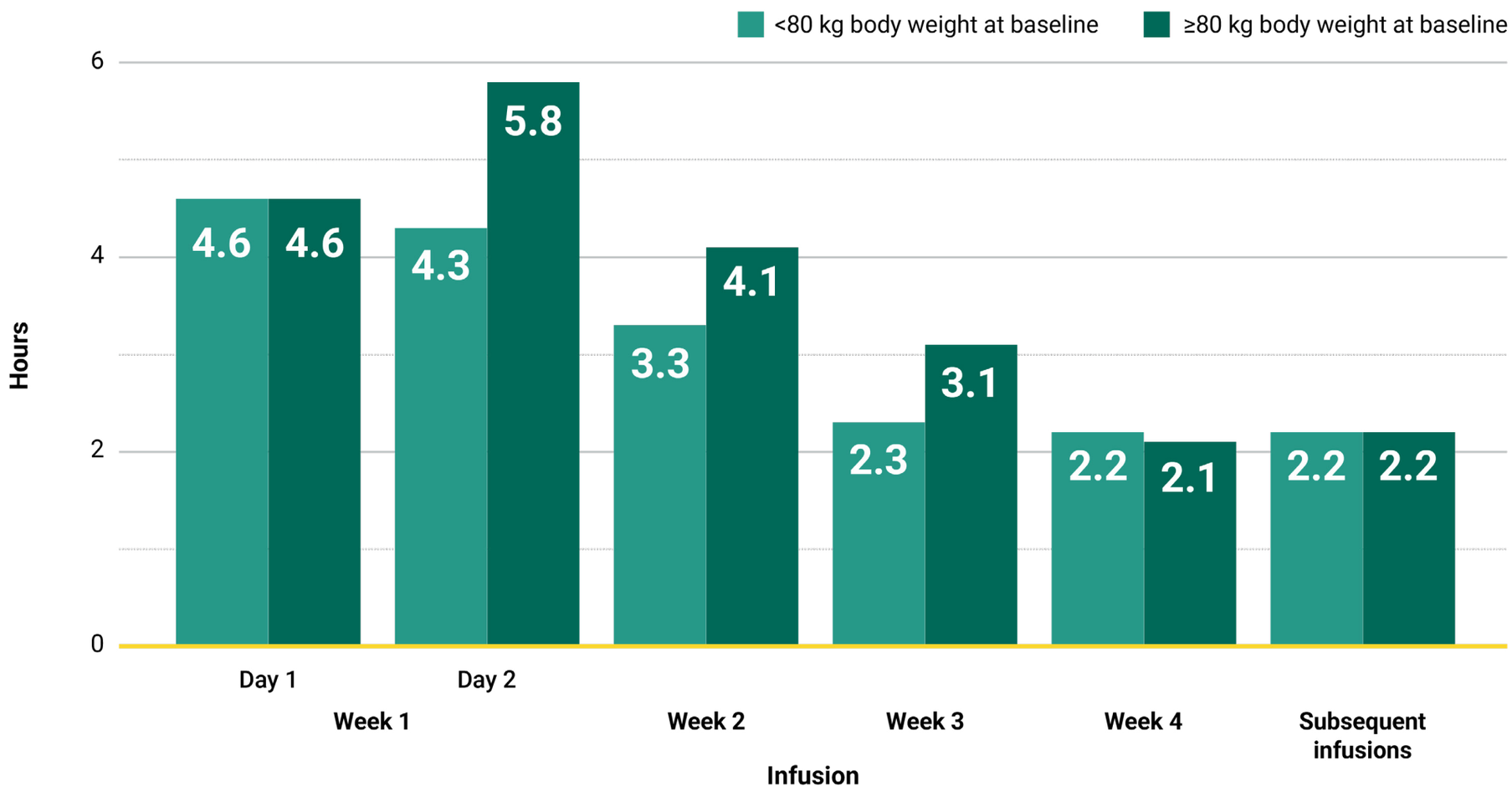
Body Weight ≥80 kg			
Week	**Dose (per 250 mL bag)**	**Initial infusion rate**	**Subsequent infusion rate***
Week 1 (split dose infusion)			
Week 1, Day 1	350 mg	50 mL/hr	75 mL/hr
Week 1, Day 2	1,050 mg	35 mL/hr	50 mL/hr
Week 2	1,400 mg	65 mL/hr	
Week 3	1,400 mg	85 mL/hr	
Week 4	1,400 mg	125 mL/hr	
Week 5	1,400 mg	125 mL/hr	
Week 6	No dose		
Week 7, and every 2 weeks thereafter	1,400 mg	125 mL/hr	

*In the absence of infusion-related reactions, increase the initial infusion rate to the subsequent infusion rate after 2 hours based on patient tolerance. Total infusion time is approximately 4 to 6 hours for Day 1 and 6 to 8 hours for Day 2. Subsequent infusion time is approximately 2 hours.

Please see full Important Safety Information. Please read full Prescribing Information for RYBREVANT® and full Prescribing Information for LAZCLUZE™.

In the MARIPOSA trial, infusion times decreased over time with RYBREVANT®[5]

Clinical trial median infusion times by hours*



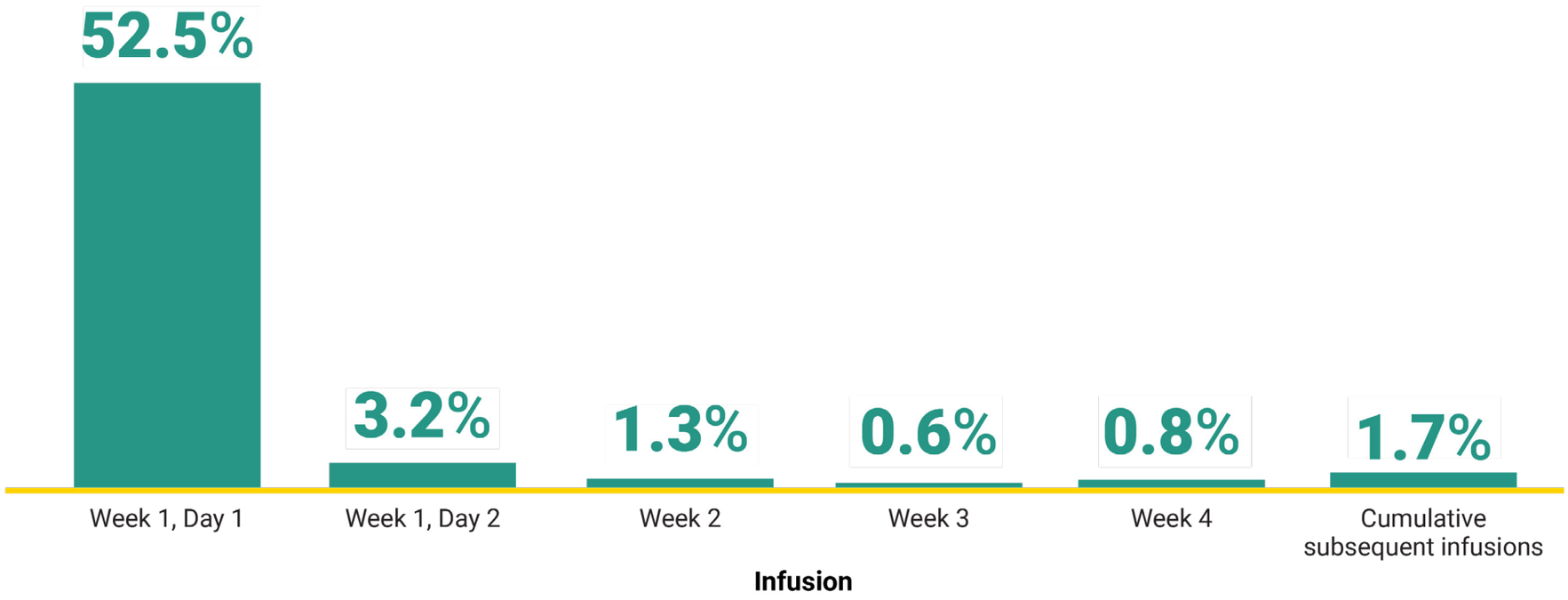
Total infusion time is approximately 4 to 6 hours for Day 1 and 6 to 8 hours for Day 2. Subsequent infusion time is approximately 2 hours.

*Data reflect results from 2-week dosing in the MARIPOSA trial.

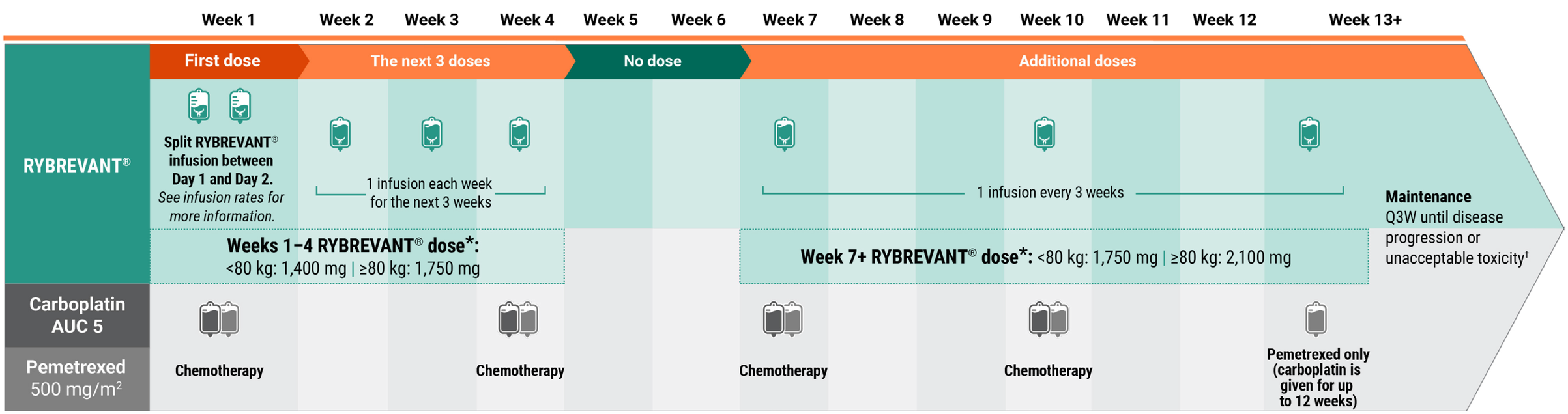
MARIPOSA IRR rates[5]

In the MARIPOSA trial, most IRRs occurred during the fiirst infusion (Week 1, Day 1) and rarely during subsequent infusions.

IRR rates per RYBREVANT® infusion (%)



Recommended dosing schedule for RYBREVANT® + chemotherapy[1]



RYBREVANT®: The recommended dosage of RYBREVANT® is based on baseline body weight and administered as an intravenous infusion after dilution.

With chemotherapy: Administer the pemetrexed infusion first, carboplatin infusion second, and the RYBREVANT® infusion last. Refer to the full Prescribing Information for pemetrexed and carboplatin for the respective dosing information.

Administer the combination in the following order: pemetrexed, carboplatin, RYBREVANT®

*Dose adjustments not required for subsequent body weight changes.
†This refers only to RYBREVANT® and pemetrexed. Carboplatin should only be administered every 3 weeks for up to 12 weeks.
AUC, area under the curve; Q3W, once every 3 weeks.

Please see full Important Safety Information. Please read full Prescribing Information for RYBREVANT® and full Prescribing Information for LAZCLUZE™.

RYBREVANT® in combination with chemotherapy administration[1]

RYBREVANT®

- **Administer the diluted RYBREVANT® solution by intravenous infusion** using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding PES filter (pore size 0.2 micrometer)
- Administration sets must be made of PU, PBD, PVC, PP, or PE
- The administration set with filter must be primed with either 5% dextrose injection or 0.9% sodium chloride injection prior to the initiation of each RYBREVANT® infusion
- **Do not infuse RYBREVANT® concomitantly in the same intravenous line with other agents**

RYBREVANT® in combination with carboplatin and pemetrexed

- **Administer RYBREVANT® in combination with carboplatin and pemetrexed infusions every 3 weeks** intravenously until disease progression or unacceptable toxicity according to the infusion rates (see **infusion rates**)
- Administer RYBREVANT® via a peripheral line on Week 1 and Week 2 given the high incidence of IRRs during initial treatment
- RYBREVANT® may be administered via a central line for subsequent weeks
- **For the initial infusion**, prepare RYBREVANT® as close to administration time as possible to allow for the possibility of extended infusion time in the event of an infusion-related reaction
- Administer the **pemetrexed infusion first,** the **carboplatin infusion second,** and the **RYBREVANT® infusion last**

IRR, infusion-related reaction; PBD, polybutadiene; PE, polyethylene; PES, polyethersulfone; PP, polypropylene; PU, polyurethane; PVC, polyvinylchloride.

Infusion rates for RYBREVANT® in combination with chemotherapy[1]

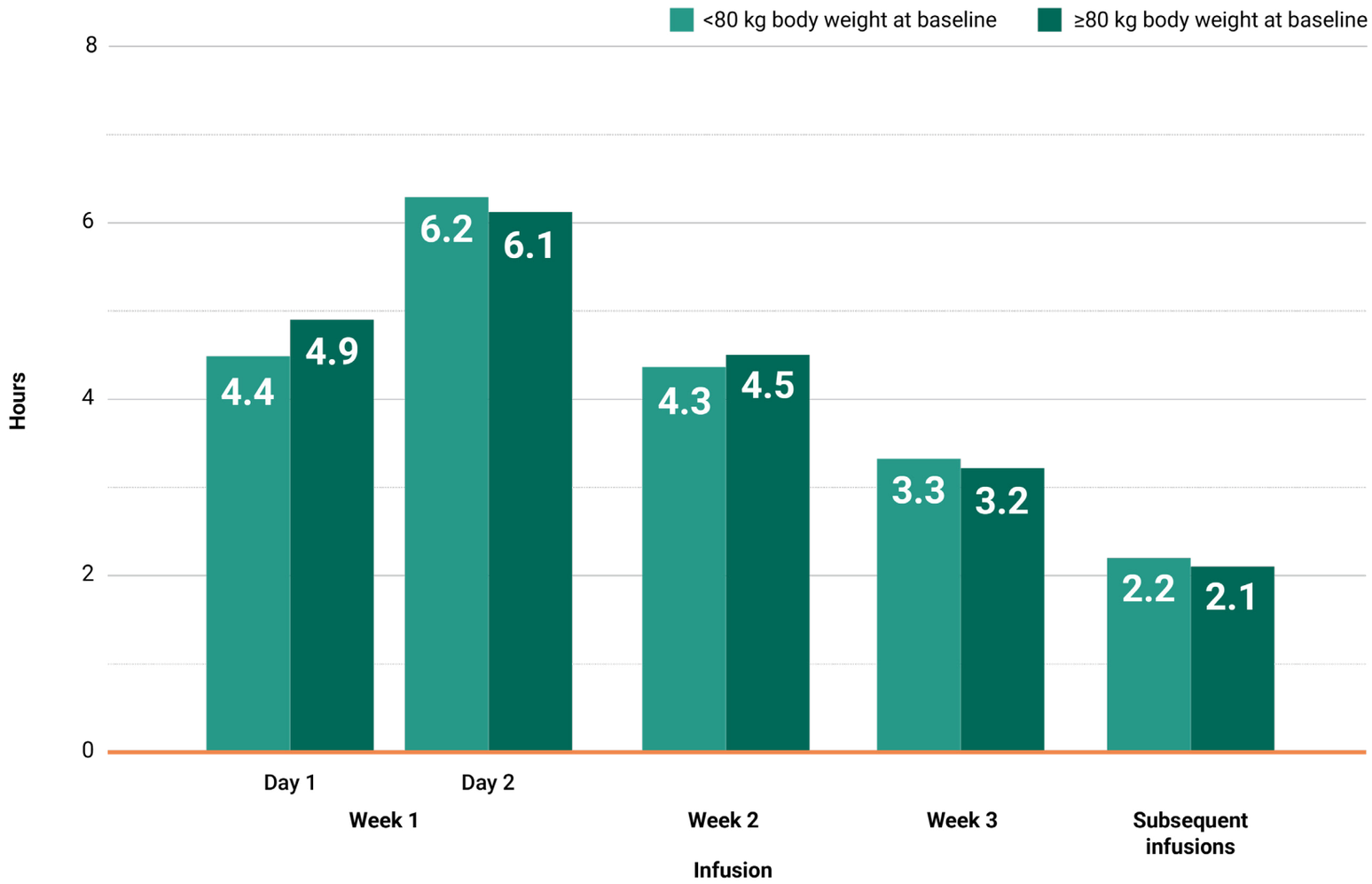
Body Weight <80 kg			
Week	**Dose (per 250 mL bag)**	**Initial infusion rate**	**Subsequent infusion rate***
Week 1 (split dose infusion)			
Week 1, Day 1	350 mg	50 mL/hr	75 mL/hr
Week 1, Day 2	1,050 mg	33 mL/hr	50 mL/hr
Week 2	1,400 mg	65 mL/hr	
Week 3	1,400 mg	85 mL/hr	
Week 4	1,400 mg	125 mL/hr	
Weeks 5 and 6	No dose		
Week 7, and every 3 weeks thereafter	1,750 mg	125 mL/hr	

Body Weight ≥80 kg			
Week	**Dose (per 250 mL bag)**	**Initial infusion rate**	**Subsequent infusion rate***
Week 1 (split dose infusion)			
Week 1, Day 1	350 mg	50 mL/hr	75 mL/hr
Week 1, Day 2	1,400 mg	25 mL/hr	50 mL/hr
Week 2	1,750 mg	65 mL/hr	
Week 3	1,750 mg	85 mL/hr	
Week 4	1,750 mg	125 mL/hr	
Weeks 5 and 6	No dose		
Week 7, and every 3 weeks thereafter	2,100 mg	125 mL/hr	

*In the absence of infusion-related reactions, increase the initial infusion rate to the subsequent infusion rate after 2 hours based on patient tolerance. Total infusion time is approximately 4 to 6 hours for Day 1 and 6 to 8 hours for Day 2. Subsequent infusion time is approximately 2 hours.

In the MARIPOSA-2 trial, infusion times decreased over time with RYBREVANT®[5]

Clinical trial median infusion times by hours*



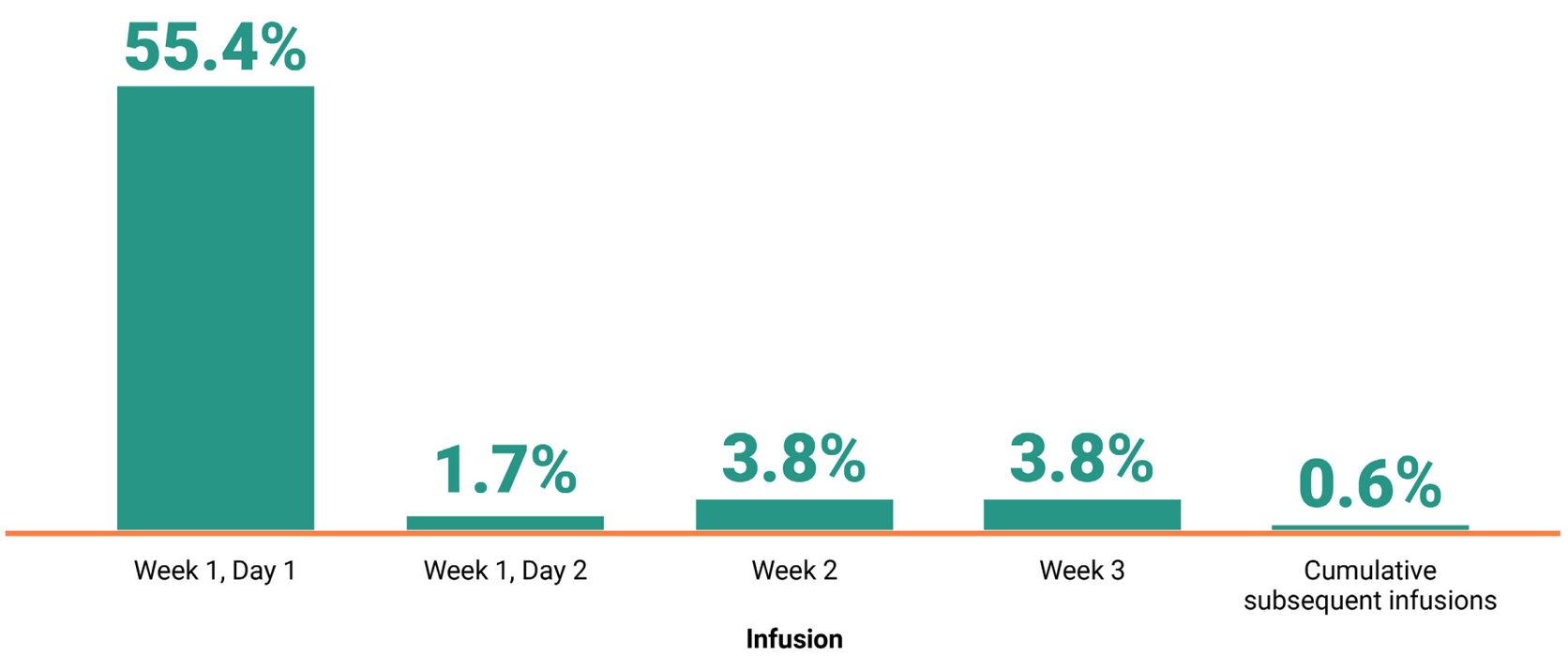
Total infusion time is approximately 4 to 6 hours for Day 1 and 6 to 8 hours for Day 2. Subsequent infusion time is approximately 2 hours.

*Data reflect results from 3-week dosing in the MARIPOSA-2 trial.[1]

MARIPOSA-2 IRR rates[5]

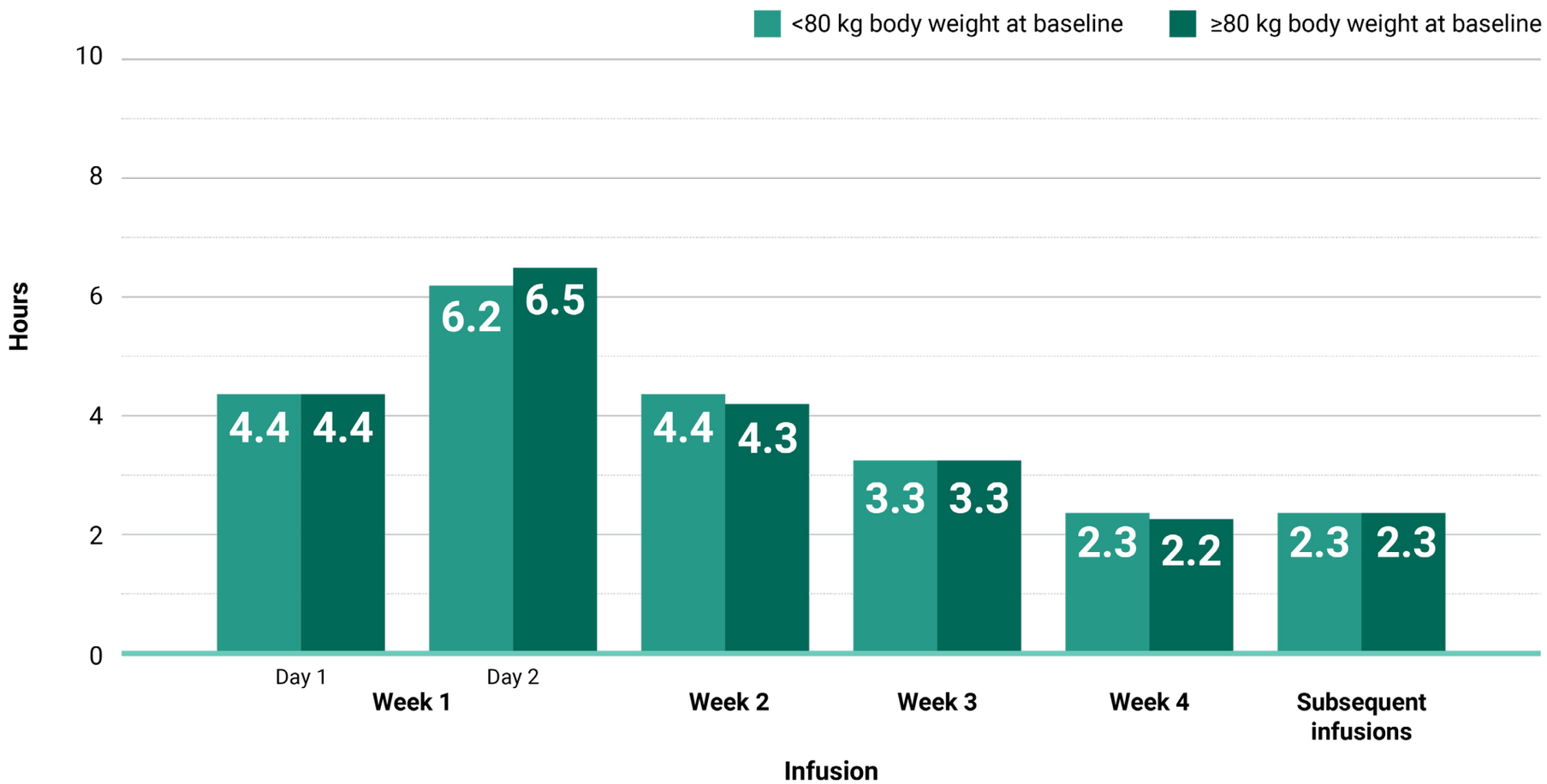
In the MARIPOSA-2 trial, most IRRs occurred during the first infusion (Week 1, Day 1) and rarely during subsequent infusions.

IRR rates per RYBREVANT® infusion (%)



In the PAPILLON trial, infusion times decreased over time with RYBREVANT®[5]

Clinical trial median infusion times by hours*



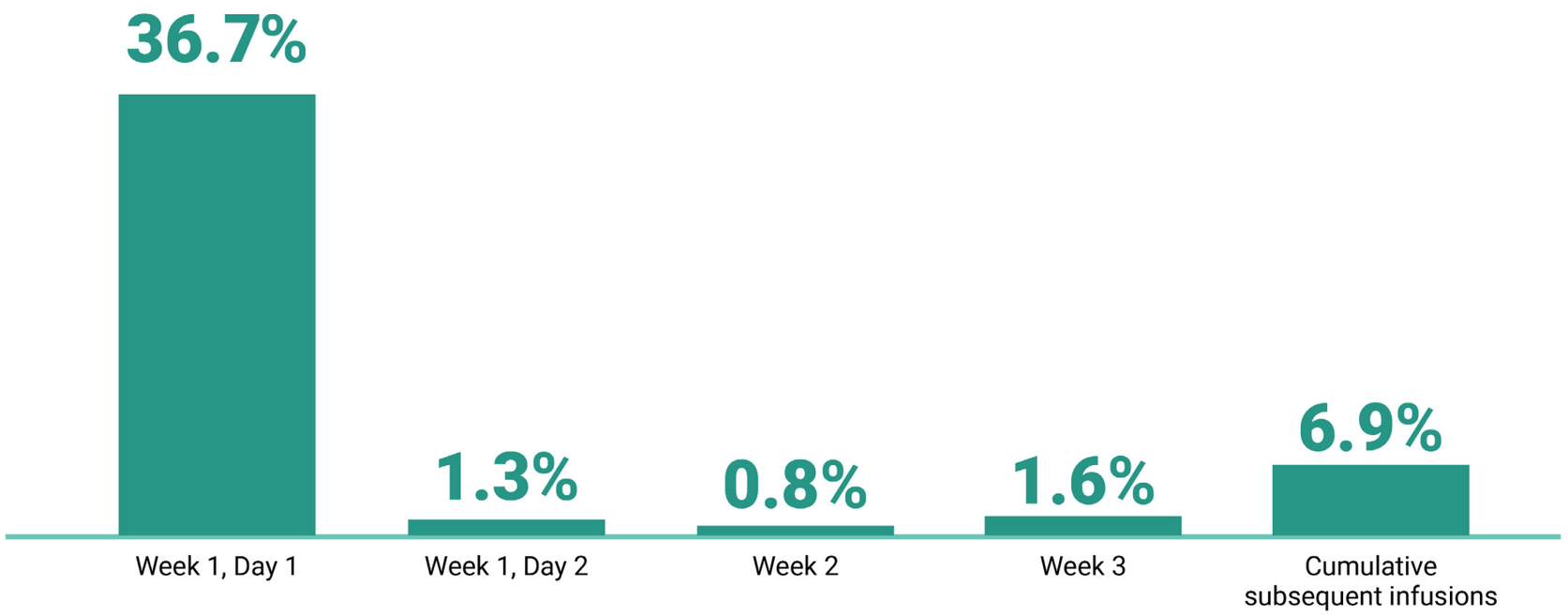
Total infusion time is approximately 4 to 6 hours for Day 1 and 6 to 8 hours for Day 2. Subsequent infusion time is approximately 2 hours.

*Data reflect results from 3-week dosing in the PAPILLON trial.[1]

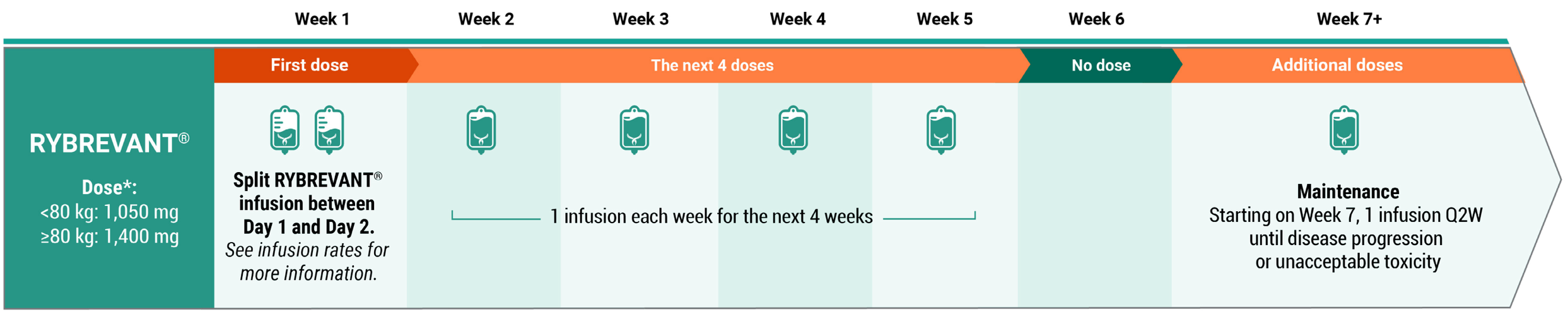
PAPILLION IRR rates[5]

In the PAPILLON trial, most IRRs occurred during the first infusion (Week 1, Day 1) and rarely during subsequent infusions.

IRR rates per RYBREVANT® infusion (%)



Recommended dosing for RYBREVANT® as a single agent[1]



The recommended dosage of RYBREVANT® is based on baseline body weight and administered as a an intravenous infusion after dilution.

*Dose adjustments not required for subsequent body weight changes.
Q2W, once every 2 weeks.

Please see full Important Safety Information. Please read full Prescribing Information for RYBREVANT® and full Prescribing Information for LAZCLUZE™.

RYBREVANT® as a single agent administration[1]

RYBREVANT®

- **Administer the diluted RYBREVANT® solution by intravenous infusion** using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding PES filter (pore size 0.2 micrometer)
- Administration sets must be made of PU, PBD, PVC, PP, or PE
- The administration set with filter must be primed with either 5% dextrose injection or 0.9% sodium chloride injection prior to the initiation of each RYBREVANT® infusion
- **Do not infuse RYBREVANT® concomitantly in the same intravenous line with other agents**

RYBREVANT® as a single agent

- **Administer RYBREVANT® as a single agent infusion every 2 weeks** intravenously according to the infusion rates (see infusion rates)
- **Administer RYBREVANT® via a peripheral line on Week 1 and Week 2,** given the high incidence of IRRs during initial treatment
- RYBREVANT® may be administered via a central line for subsequent weeks
- **For the initial infusion**, prepare RYBREVANT® as close to administration time as possible to allow for the possibility of extended infusion time in the event of an infusion-related reaction

IRR, infusion-related reaction; PBD, polybutadiene; PE, polyethylene; PES, polyethersulfone; PP, polypropylene; PU, polyurethane; PVC, polyvinylchloride.

Infusion rates for RYBREVANT® as a single agent[1]

Body Weight <80 kg			
Week	**Dose (per 250 mL bag)**	**Initial infusion rate**	**Subsequent infusion rate***
Week 1 (split dose infusion)			
Week 1, Day 1	350 mg	50 mL/hr	75 mL/hr
Week 1, Day 2	700 mg	50 mL/hr	75 mL/hr
Week 2	1,050 mg	85 mL/hr	
Week 3	1,050 mg	125 mL/hr	
Week 4	1,050 mg	125 mL/hr	
Week 5	1,050 mg	125 mL/hr	
Week 6	No dose		
Week 7, and every 2 weeks thereafter	1,050 mg	125 mL/hr	

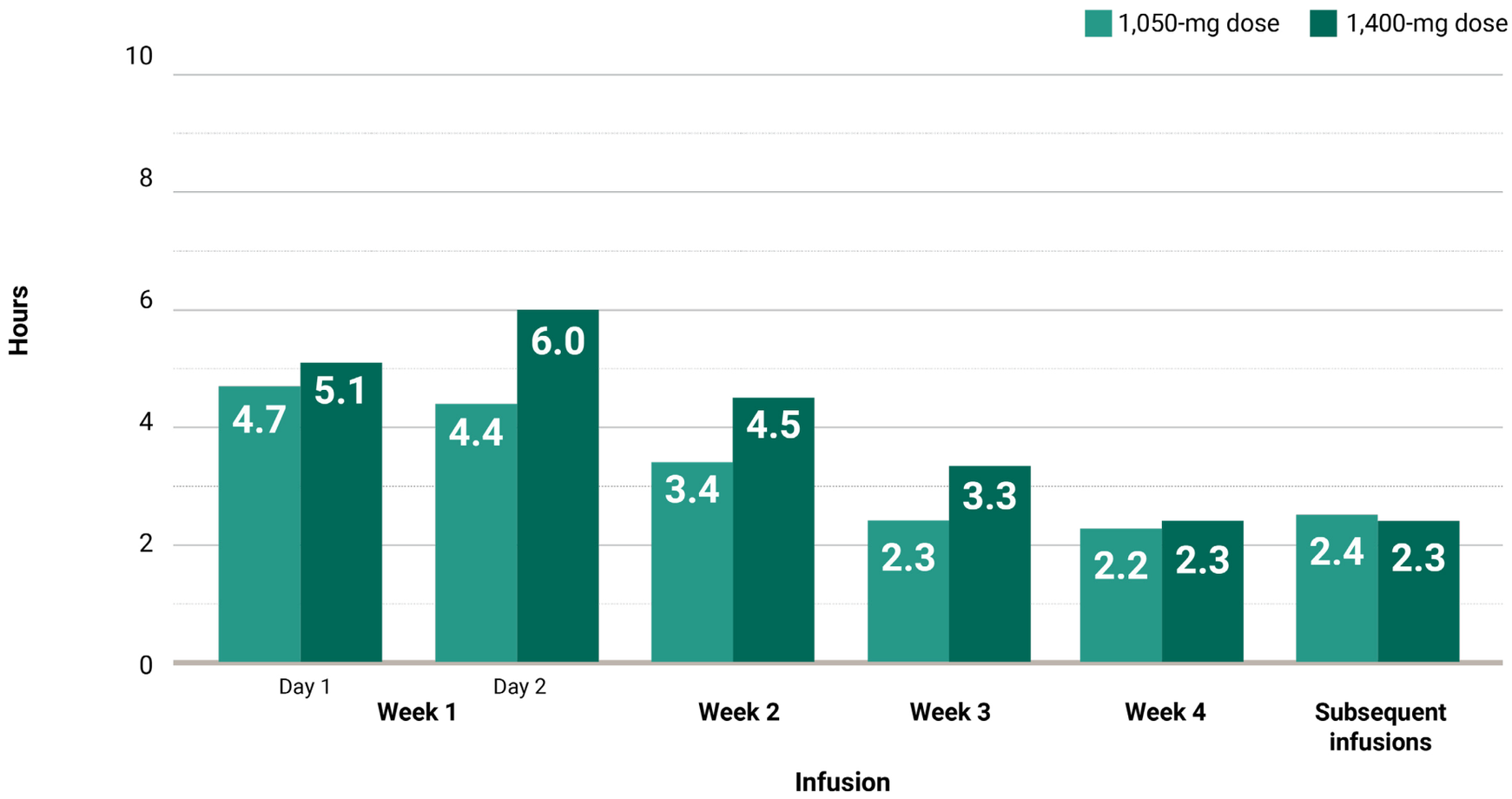
Body Weight ≥80 kg			
Week	**Dose (per 250 mL bag)**	**Initial infusion rate**	**Subsequent infusion rate***
Week 1 (split dose infusion)			
Week 1, Day 1	350 mg	50 mL/hr	75 mL/hr
Week 1, Day 2	1,050 mg	35 mL/hr	50 mL/hr
Week 2	1,400 mg	65 mL/hr	
Week 3	1,400 mg	85 mL/hr	
Week 4	1,400 mg	125 mL/hr	
Week 5	1,400 mg	125 mL/hr	
Week 6	No dose		
Week 7, and every 2 weeks thereafter	1,400 mg	125 mL/hr	

*In the absence of infusion-related reactions, increase the initial infusion rate to the subsequent infusion rate after 2 hours based on patient tolerance. Total infusion time is approximately 4 to 6 hours for Day 1 and 6 to 8 hours for Day 2. Subsequent infusion time is approximately 2 hours.

Please see full Important Safety Information. Please read full Prescribing Information for RYBREVANT® and full Prescribing Information for LAZCLUZE™.

In the CHRYSALIS trial, infusion times decreased over time with RYBREVANT®[5]

Clinical trial median infusion times by hours*

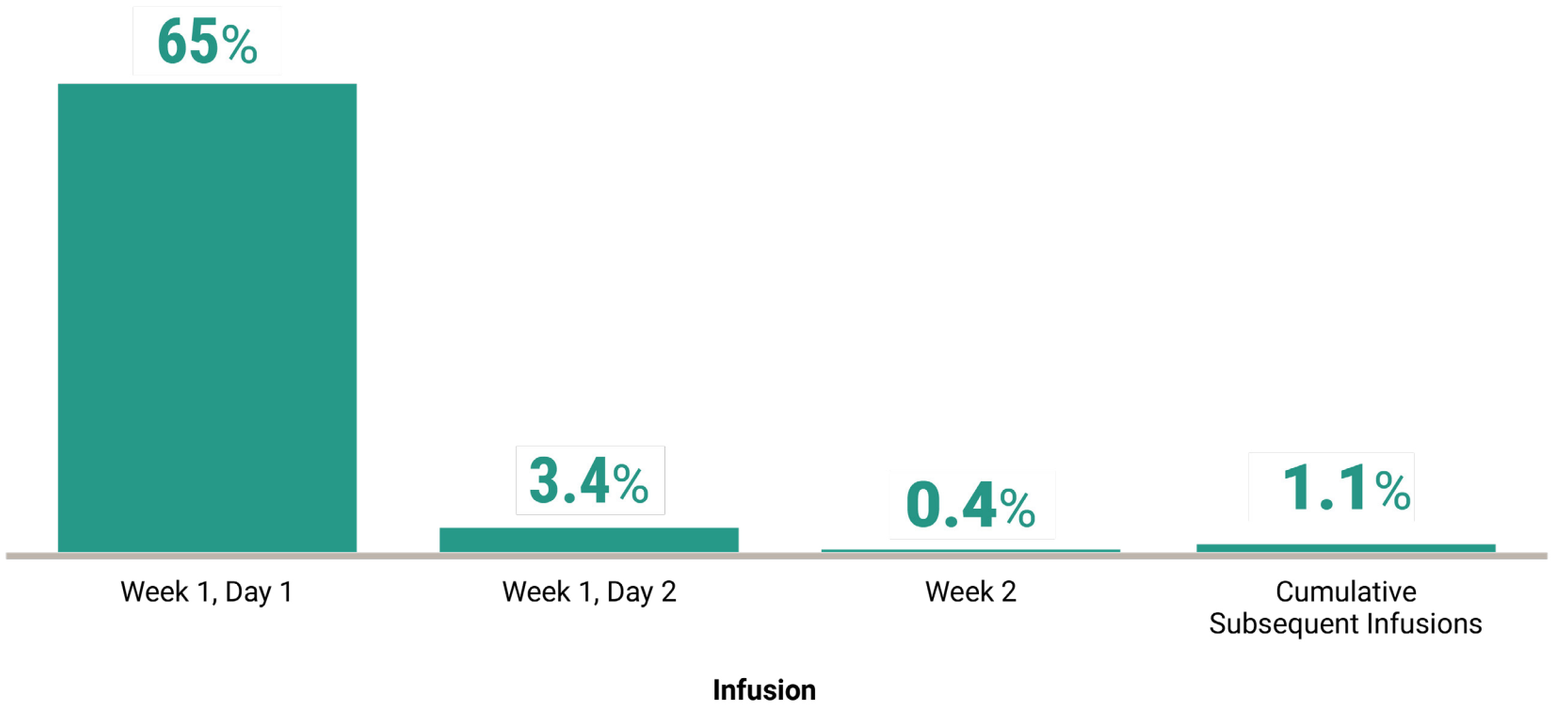


*Data reflect results from 2-week dosing in the CHRYSALIS trial.[1]

CHRYSALIS IRR rates[1]

In the CHRYSALIS trial, most IRRs occurred during the first infusion (Week 1, Day 1) and rarely during subsequent infusions.

IRR rates per RYBREVANT® infusion (%)



Recommended premedications for RYBREVANT®[1]

Medication	Dose	Route of Administration	Dosing Window Prior to RYBREVANT® Administration	Frequency
Antihistamine	Diphenhydramine (25 to 50 mg) or equivalent	Intravenous	15 to 30 minutes	All doses
		Oral	30 to 60 minutes	
Antipyretic	Acetaminophen (650 to 1,000 mg)	Intravenous	15 to 30 minutes	All doses
		Oral	30 to 60 minutes	
Glucocorticoid	Dexamethasone (20 mg) or equivalent	Intravenous	45 to 60 minutes	Week 1, Day 1
Glucocorticoid	Dexamethasone (10 mg) or equivalent	Intravenous	45 to 60 minutes	Week 1, Day 2 (optional for subsequent doses)

- Due to the risk of IRR, administer premedications prior to initial infusion of RYBREVANT® (Week 1, Day 1 and 2) as described in the table above
- Glucocorticoid administration is required at the initial dose at Week 1, Days 1 and 2 dose only and upon reinitiation after prolonged dose interruptions, then as necessary for subsequent infusions
- Administer both antihistamine and antipyretic prior to all infusions
- Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT® based on severity
- If an anaphylactic reaction occurs, permanently discontinue RYBREVANT®

IRR, infusion-related reaction.

Concomitant medications[1]

VTE prophylaxis

When initiating treatment with RYBREVANT® in combination with LAZCLUZE™, administer anticoagulant prophylaxis to prevent VTE events for the **first 4 months** of treatment.

- The use of Vitamin K antagonists is not recommended
- If there are no signs or symptoms of VTE during the first 4 months of treatment, consider discontinuation of anticoagulant prophylaxis at the discretion of the healthcare provider

Dermatologic ARs prophylaxis

To reduce the risk of dermatologic ARs, when initiating treatment with RYBREVANT in combination with LAZCLUZE™:

- Administer alcohol-free (eg, isopropanol-free, ethanol-free) emollient cream
- Encourage patients to limit sun exposure during and for 2 months after treatment, to wear protective clothing and use broad-spectrum UVA/UVB sunscreen
- Consider prophylactic measures (eg, use of oral antibiotics)

Refer to the full **Prescribing Information** for LAZCLUZE™ for information about concomitant medications.

Proactive therapy management is recommended and may help reduce the risk and severity of select ARs

AR, adverse reaction; UVA, ultraviolet A; UVB, ultraviolet B; VTE, venous thromboembolism.

Monitoring & management[1,2]

Recommended RYBREVANT® dose reductions for ARs

Dose reductions for ARs			
Dose at which the AR occurred	**1st Dose Reduction**	**2nd Dose Reduction**	**3rd Dose Reduction**
1,050 mg	700 mg	350 mg	Discontinue RYBREVANT®
1,400 mg	1,050 mg	700 mg	
1,750 mg	1,400 mg	1,050 mg	
2,100 mg	1,750 mg	1,400 mg	

Recommended LAZCLUZE™ dose reductions for ARs

Dose reductions for ARs			
Dose at which the AR occurred	**1st Dose Reduction**	**2nd Dose Reduction**	**3rd Dose Reduction**
240 mg once daily (one 240 mg tablet)	160 mg once daily (two 80 mg tablets)	80 mg once daily (one 80 mg tablet)	Discontinue LAZCLUZE™

Monitoring & management (cont'd)

Adverse event severity scale[6]

Based on the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.*

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)†	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL‡	Life-threatening consequences; urgent intervention indicated	Death related to adverse event

*CTCAE definition may differ from the Prescribing Information.
†Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
‡Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Monitoring & management (cont'd)

Dosage modifications and management for ARs for RYBREVANT® + LAZCLUZE™[1,2]

For RYBREVANT® + LAZCLUZE™ refer to **both** the RYBREVANT® and LAZCLUZE™ recommendations. For RYBREVANT® + chemotherapy or RYBREVANT® as a single agent, refer only to the RYBREVANT® recommendations.

Adverse Reaction	Severity	Dosage Modifications
IRR	**Grade 1 to 2**	**RYBREVANT®** • Interrupt RYBREVANT® infusion if IRR is suspected and monitor patient until reaction symptoms resolve • Resume the infusion at 50% of the infusion rate at which the reaction occurred • If there are no additional symptoms after 30 minutes, the infusion rate may be escalated • Include corticosteroid with premedications for subsequent dose
	Grade 3	**RYBREVANT®** • Interrupt RYBREVANT® infusion and administer supportive care medications. Continuously monitor patient until reaction symptoms resolve • Resume the infusion at 50% of the infusion rate at which the reaction occurred • If there are no additional symptoms after 30 minutes, the infusion rate may be escalated • Include corticosteroid with premedications for subsequent dose. For recurrent Grade 3, permanently discontinue RYBREVANT®
	Grade 4 or any Grade anaphylaxis/ anaphylactic reactions	**RYBREVANT®** • Permanently discontinue RYBREVANT®

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Monitoring & management (cont'd)

Dosage modifications and management for ARs for RYBREVANT® + LAZCLUZE™[1,2]

For RYBREVANT® + LAZCLUZE™ refer to **both** the RYBREVANT® and LAZCLUZE™ recommendations. For RYBREVANT® + chemotherapy or RYBREVANT® as a single agent, refer only to the RYBREVANT® recommendations.

Adverse Reaction	Severity	Dosage Modifications
ILD/pneumonitis	**Any Grade**	**RYBREVANT®** • Withhold RYBREVANT® if ILD/pneumonitis is suspected • Permanently discontinue RYBREVANT® if ILD/pneumonitis is confirmed **LAZCLUZE™** • Withhold LAZCLUZE™ and RYBREVANT® if ILD/pneumonitis is suspected • Permanently discontinue LAZCLUZE™ and RYBREVANT® if ILD/pneumonitis is confirmed
VTE events (applies to RYBREVANT® + LAZCLUZE™ combination only)	**Grade 2 or 3**	**RYBREVANT® + LAZCLUZE™** • Withhold RYBREVANT® and LAZCLUZE™ • Administer anticoagulant treatment as clinically indicated • Once anticoagulant treatment has been initiated, resume RYBREVANT® and LAZCLUZE™ at the same dose level, at the discretion of the healthcare provider
	Grade 4 or recurrent Grade 2 or 3 despite therapeutic level anticoagulation	**RYBREVANT® + LAZCLUZE™** • Withhold LAZCLUZE™ and permanently discontinue RYBREVANT® • Administer anticoagulant treatment as clinically indicated • Once anticoagulant treatment has been initiated, treatment can continue with LAZCLUZE™ at the same dose level at the discretion of the healthcare provider

ILD, interstitial lung disease.

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Monitoring & management (cont'd)

Dosage modifications and management for ARs for RYBREVANT® + LAZCLUZE™[1,2]

For RYBREVANT® + LAZCLUZE™ refer to **both** the RYBREVANT® and LAZCLUZE™ recommendations. For RYBREVANT® + chemotherapy or RYBREVANT® as a single agent, refer only to the RYBREVANT® recommendations.

Adverse Reaction	Severity	Dosage Modifications
Dermatologic ARs (including dermatitis acneiform, pruritus, dry skin)	**Grade 1**	**RYBREVANT®** • Initiate supportive care management • Reassess after 2 weeks; if rash does not improve, consider dose reduction **LAZCLUZE™** • Initiate supportive care management
	Grade 2	**RYBREVANT®** • Initiate supportive care management • Reassess after 2 weeks; if rash does not improve, consider dose reduction **LAZCLUZE™** • Initiate supportive care management • If there is no improvement after 2 weeks, reduce RYBREVANT® dose and continue LAZCLUZE™ at the same dose • Reassess every 2 weeks; if no improvement, reduce LAZCLUZE™ dose until ≤Grade 1, then may resume previous dose of LAZCLUZE™ at the discretion of the healthcare provider

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Monitoring & management (cont'd)

Dosage modifications and management for ARs for RYBREVANT® + LAZCLUZE™[1,2]

For RYBREVANT® + LAZCLUZE™ refer to **both** the RYBREVANT® and LAZCLUZE™ recommendations. For RYBREVANT® + chemotherapy or RYBREVANT® as a single agent, refer only to the RYBREVANT® recommendations.

Adverse Reaction	Severity	Dosage Modifications
Dermatologic ARs (cont'd) (including dermatitis acneiform, pruritus, dry skin)	**Grade 3**	**RYBREVANT®** • Withhold RYBREVANT® and initiate supportive care management • Upon recovery to ≤Grade 2, resume RYBREVANT® at reduced dose • If no improvement within 2 weeks, permanently discontinue treatment **LAZCLUZE™** • Withhold LAZCLUZE™ and RYBREVANT® • Initiate supportive care management • Upon recovery to ≤Grade 2, resume LAZCLUZE™ at the same dose or consider dose reduction; resume RYBREVANT® at a reduced dose • If there is no improvement within 2 weeks, permanently discontinue both LAZCLUZE™ and RYBREVANT®
	Grade 4 (including severe bullous, blistering, or exfoliating skin conditions, including TEN for RYBREVANT®)	**RYBREVANT®** • Permanently discontinue RYBREVANT® **LAZCLUZE™** • Initiate supportive care management • Permanently discontinue RYBREVANT® • Withhold LAZCLUZE™ until recovery to ≤Grade 2 or baseline • Upon recovery to ≤Grade 2, resume LAZCLUZE™ at a reduced dose, at the discretion of the healthcare provider

TEN, toxic epidermal necrolysis.

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Please see full Important Safety Information. Please read full Prescribing Information for RYBREVANT® and full Prescribing Information for LAZCLUZE™.

Monitoring & management (cont'd)

Dosage modifications and management for ARs for RYBREVANT® + LAZCLUZE™[1,2]

For RYBREVANT® + LAZCLUZE™ refer to **both** the RYBREVANT® and LAZCLUZE™ recommendations. For RYBREVANT® + chemotherapy or RYBREVANT® as a single agent, refer only to the RYBREVANT® recommendations.

Adverse Reaction	Severity	Dosage Modifications
Other ARs	**Grade 3**	**RYBREVANT®** • Withhold RYBREVANT® until recovery to ≤Grade 1 or baseline • Resume at the same dose if recovery occurs within 1 week • Resume at reduced dose if recovery occurs after 1 week but within 4 weeks • Permanently discontinue if recovery does not occur within 4 weeks **LAZCLUZE™** • Withhold LAZCLUZE™ and RYBREVANT® until the adverse reaction resolves to ≤Grade 1 or baseline • Resume both drugs at a reduced dose or LAZCLUZE™ alone • Consider permanently discontinuing both LAZCLUZE™ and RYBREVANT® if recovery does not occur within 4 weeks

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Monitoring & management (cont'd)

Dosage modifications and management for ARs for RYBREVANT® + LAZCLUZE™[1,2]

For RYBREVANT® + LAZCLUZE™ refer to **both** the RYBREVANT® and LAZCLUZE™ recommendations. For RYBREVANT® + chemotherapy or RYBREVANT® as a single agent, refer only to the RYBREVANT® recommendations.

Adverse Reaction	Severity	Dosage Modifications
Other ARs (cont'd)	**Grade 4**	**RYBREVANT®** • Withhold RYBREVANT® until recovery to ≤Grade 1 or baseline • Resume at reduced dose if recovery occurs within 4 weeks • Permanently discontinue if recovery does not occur within 4 weeks • Permanently discontinue for recurrent Grade 4 reactions **LAZCLUZE™** • Withhold LAZCLUZE™ and RYBREVANT® until the adverse reaction resolves to ≤Grade 1 or baseline • Resume both drugs at a reduced dose or LAZCLUZE™ alone • Consider permanently discontinuing both LAZCLUZE™ and RYBREVANT® if recovery does not occur within 4 weeks

Recommended dosage modifications for ARs for RYBREVANT® in combination with LAZCLUZE™[1]

When administering RYBREVANT® in combination with LAZCLUZE™, if there is an AR requiring dose reduction after withholding treatment and resolution, reduce the dose of RYBREVANT® first.

Refer to the full **Prescribing Information** for LAZCLUZE™ for information about dosage modifications for LAZCLUZE™.

Recommended dosage modifications for ARs for RYBREVANT® in combination with carboplatin and pemetrexed[1]

When administering RYBREVANT® in combination with carboplatin and pemetrexed, modify the dosage of one or more drugs. Withhold or discontinue RYBREVANT® as shown in the table on pages 25-30.

Refer to Prescribing Information for carboplatin and pemetrexed for additional dosage modification information.

Prophylaxis is recommended to prevent VTE

Drug-related prophylaxis for VTE[1]

Prophylactic treatment with an anticoagulation medicine is recommended for the **first 4 months** of treatment with RYBREVANT® + LAZCLUZE™.

- The use of Vitamin K antagonists is not recommended
- If there are no signs or symptoms of VTE during the first 4 months of treatment, consider discontinuation of anticoagulant prophylaxis at the discretion of the healthcare provider

VTE, which includes DVT and PE, is a key cause of morbidity among patients with lung cancer[7]

People living with cancer are at **9 times the risk** of developing VTE compared with the general population[8]

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommendations for cancer-associated VTE disease[9]

Anticoagulant options for VTE prophylaxis for ambulatory patients with cancer include direct oral anticoagulants (DOACs) and low molecular weight heparins (LMWHs).*†‡

Learn more about proactive strategies at www.RYBREVANThcp.com/proactive-supportive-care/

*Recommendations derived from clinical trials of ambulatory patients with cancer with high thrombosis risk (>18 years, Khorana VTE Risk Score of ≥2, initiating new course of chemotherapy) and are not included in product labeling. Prophylaxis duration should be 6 months or longer if risk persists.
†Always refer to the NCCN Guidelines® for the comprehensive and most up-to-date recommendations on cancer-associated VTE when considering prophylaxis.
‡When using RYBREVANT® in combination with LAZCLUZE™, please refer to the Prescribing Information for VTE prophylaxis recommendation.
DVT, deep vein thrombosis; NCCN, National Comprehensive Cancer Network; PE, pulmonary embolism.

Please see full Important Safety Information. Please read full Prescribing Information for RYBREVANT® and full Prescribing Information for LAZCLUZE™.

Patient counseling information[1,2]

Advise the patient to read the FDA-approved patient labeling (Patient Information)

IRRs	Advise patients that RYBREVANT® can cause IRRs, including anaphylaxis. The majority of IRRs occurred with the first infusion. Advise patients to alert their healthcare provider immediately for any signs or symptoms of IRRs.
ILD/Pneumonitis	Advise patients that RYBREVANT® can cause ILD/pneumonitis. Advise patients to immediately contact their healthcare provider for new or worsening respiratory symptoms.
VTE Events with Concomitant Use with LAZCLUZE™	When RYBREVANT® is used in combination with LAZCLUZE™, advise patients of the risks of serious and life threatening VTE events, including DVT and PE. Advise patients that prophylactic anticoagulants are recommended to be used for the first 4 months of treatment. Advise patients to immediately contact their healthcare provider for signs and symptoms of VTE.
Dermatologic ARs	Advise patients that RYBREVANT® can cause dermatologic ARs. Advise patients to apply alcohol-free (eg, isopropanol-free, ethanol-free) emollient cream to reduce the risk of skin reactions. Consider prophylactic measures (eg, use of oral antibiotics) to reduce the risk of dermatologic ARs. Advise patients to limit direct sun exposure during and for 2 months after treatment, to use broad spectrum UVA/UVB sunscreen, and to wear protective clothing during treatment with RYBREVANT®.
Ocular Toxicity	Advise patients that RYBREVANT® can cause ocular toxicity. Advise patients to contact their ophthalmologist if they develop eye symptoms and advise discontinuation of contact lenses until symptoms are evaluated.
Paronychia/Nail Toxicity	Advise patients that RYBREVANT® can cause paronychia. Advise patients to contact their healthcare provider for signs or symptoms of paronychia.
Embryo-Fetal Toxicity	Advise females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment with RYBREVANT® and for 3 months after the last dose, and to inform their healthcare provider of a known or suspected pregnancy.
Lactation	Advise women not to breastfeed during treatment with RYBREVANT® and for 3 months after the last dose.
Infertility	Advise males and females of reproductive potential of the potential risk for impaired fertility with LAZCLUZE™.

Please see full Important Safety Information. Please read full Prescribing Information for RYBREVANT® and full Prescribing Information for LAZCLUZE™.

Infusion checklist[1]

Pre-infusion

Prior to initial infusion of RYBREVANT® (Week 1, Days 1 and 2), administer **premedication** to reduce the risk of IRRs.

- Administer both antihistamine and antipyretic prior to all infusions
- Glucocorticoid administration is required for Week 1, Day 1 and 2 dose only and as necessary for subsequent infusions
- Do not infuse RYBREVANT® concomitantly in the same intravenous line with other agents
- Administer RYBREVANT® via a peripheral line on Week 1 and Week 2 given the high incidence of IRRs during initial treatment. RYBREVANT® may be administered via a central line for subsequent weeks

For additional proactive strategies to help support your patients throughout treatment, visit **www.RYBREVANThcp.com/proactive-supportive-care/**

During the infusion

Administer RYBREVANT® infusion intravenously according to the infusion rates in the charts within the section for the correct regimen.

Monitor patients for any signs and symptoms of infusion reactions during RYBREVANT® infusion in a setting where cardiopulmonary resuscitation medication and equipment are available.

- Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT® based on severity
- If an anaphylactic reaction occurs, permanently discontinue RYBREVANT®

Reach out to an Oncology Clinical Educator (OCE) at www.RYBREVANThcp.com/contact-a-representative

OCEs are oncology nurses employed by Johnson & Johnson to provide product-specific and disease state education information to oncology patient-care team members, patient support groups, and advocacy organizations.

IRR, infusion-related reaction.

References

References: 1. RYBREVANT® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** LAZCLUZE™ [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **3.** Yun J, Hong MH, Kim SY, et al. YH25448, an irreversible EGFR-TKI with potent intracranial activity in EGFR mutant non–small cell lung cancer. *Clin Cancer Res*. 2019;25(8):2575-2587. **4.** Cho BC, Simi A, Sabari J, et al. Amivantamab, an epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition factor (MET) bispecific antibody, designed to enable multiple mechanisms of action and broad clinical applications. *Clin Lung Cancer*. 2023;24(2):89-97. **5.** Data on file. Janssen Biotech, Inc. **6.** US Department of Health and Human Services. National Cancer Institute. Common terminology criteria for adverse events (CTCAE). Version 5.0. Published November 27, 2017. Accessed June 7, 2024. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf **7.** Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol*. 2020;38(5):496-520. **8.** Mulder FI, Horváth-Puhó, van Es N, et al. Venous thromboembolism in cancer patients: a population-based cohort study. *Blood*. 2021;137(14):1959-1969. **9.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Cancer-Associated Venous Thromboembolic Disease V.1.2025 © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed February 27, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Indications and Important Safety Information

INDICATIONS

RYBREVANT® (amivantamab-vmjw) is indicated:

- in combination with LAZCLUZE™ (lazertinib) for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations, as detected by an FDA-approved test.
- in combination with carboplatin and pemetrexed for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with an EGFR tyrosine kinase inhibitor.
- in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test.
- as a single agent for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

RYBREVANT® can cause infusion-related reactions (IRR) including anaphylaxis; signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting. The median time to IRR onset is approximately 1 hour.

RYBREVANT® with LAZCLUZE™

RYBREVANT® in combination with LAZCLUZE™ can cause infusion-related reactions. In MARIPOSA (n=421), IRRs occurred in 63% of patients treated with RYBREVANT® in combination with LAZCLUZE™, including Grade 3 in 5% and Grade 4 in 1% of patients. The incidence of infusion modifications due to IRR was 54% of patients, and IRRs leading to dose reduction of RYBREVANT® occurred in 0.7% of patients. Infusion-related reactions leading to permanent discontinuation of RYBREVANT® occurred in 4.5% of patients receiving RYBREVANT® in combination with LAZCLUZE™.

RYBREVANT® with Carboplatin and Pemetrexed

Based on the pooled safety population (n=281), IRR occurred in 50% of patients treated with RYBREVANT® in combination with carboplatin and pemetrexed, including Grade 3 (3.2%) adverse reactions. The incidence of infusion modifications due to IRR was 46%, and 2.8% of patients permanently discontinued RYBREVANT® due to IRR.

Indications and Important Safety Information (cont'd)

RYBREVANT® as a Single Agent

In CHRYSALIS (n=302), IRR occurred in 66% of patients treated with RYBREVANT®. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62% and 1.3% of patients permanently discontinued RYBREVANT® due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT® as recommended. Administer RYBREVANT® via a peripheral line on Week 1 and Week 2 to reduce the risk of infusion-related reactions. Monitor patients for signs and symptoms of infusion reactions during RYBREVANT® infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT® based on severity. If an anaphylactic reaction occurs, permanently discontinue RYBREVANT®.

Interstitial Lung Disease/Pneumonitis

RYBREVANT® can cause severe and fatal interstitial lung disease (ILD)/pneumonitis.

RYBREVANT® with LAZCLUZE™

In MARIPOSA, ILD/pneumonitis occurred in 3.1% of patients treated with RYBREVANT® in combination with LAZCLUZE™, including Grade 3 in 1.0% and Grade 4 in 0.2% of patients. There was one fatal case (0.2%) of ILD/pneumonitis and 2.9% of patients permanently discontinued RYBREVANT® and LAZCLUZE™ due to ILD/pneumonitis.

RYBREVANT® with Carboplatin and Pemetrexed

Based on the pooled safety population, ILD/pneumonitis occurred in 2.1% treated with RYBREVANT® in combination with carboplatin and pemetrexed with 1.8% of patients experiencing Grade 3 ILD/pneumonitis. 2.1% discontinued RYBREVANT® due to ILD/pneumonitis.

RYBREVANT® as a Single Agent

In CHRYSALIS, ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT®, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) permanently discontinued RYBREVANT® due to ILD/pneumonitis.

Indications and Important Safety Information (cont'd)

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). For patients receiving RYBREVANT® in combination with LAZCLUZE™, immediately withhold both drugs in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed. For patients receiving RYBREVANT® as a single agent or in combination with carboplatin and pemetrexed, immediately withhold RYBREVANT® in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed.

Venous Thromboembolic (VTE) Events with Concomitant Use of RYBREVANT® and LAZCLUZE™

RYBREVANT® in combination with LAZCLUZE™ can cause serious and fatal venous thromboembolic (VTE) events, including deep vein thrombosis and pulmonary embolism. The majority of these events occurred during the first four months of therapy.

In MARIPOSA, VTEs occurred in 36% of patients receiving RYBREVANT® in combination with LAZCLUZE™, including Grade 3 in 10% and Grade 4 in 0.5% of patients. On-study VTEs occurred in 1.2% of patients (n=5) while receiving anticoagulation therapy. There were two fatal cases of VTE (0.5%), 9% of patients had VTE leading to dose interruptions of RYBREVANT®, and 7% of patients had VTE leading to dose interruptions of LAZCLUZE™; 1% of patients had VTE leading to dose reductions of RYBREVANT®, and 0.5% of patients had VTE leading to dose reductions of LAZCLUZE™; 3.1% of patients had VTE leading to permanent discontinuation of RYBREVANT®, and 1.9% of patients had VTE leading to permanent discontinuation of LAZCLUZE™. The median time to onset of VTEs was 84 days (range: 6 to 777).

Administer prophylactic anticoagulation for the first four months of treatment. The use of Vitamin K antagonists is not recommended. Monitor for signs and symptoms of VTE events and treat as medically appropriate.

Withhold RYBREVANT® and LAZCLUZE™ based on severity. Once anticoagulant treatment has been initiated, resume RYBREVANT® and LAZCLUZE™ at the same dose level at the discretion of the healthcare provider. In the event of VTE recurrence despite therapeutic anticoagulation, permanently discontinue RYBREVANT® and continue treatment with LAZCLUZE™ at the same dose level at the discretion of the healthcare provider.

Dermatologic Adverse Reactions

RYBREVANT® can cause severe rash including toxic epidermal necrolysis (TEN), dermatitis acneiform, pruritus, and dry skin.

RYBREVANT® with LAZCLUZE™

In MARIPOSA, rash occurred in 86% of patients treated with RYBREVANT® in combination with LAZCLUZE™, including Grade 3 in 26% of patients. The median time to onset of rash was 14 days (range: 1 to 556 days). Rash leading to dose interruptions occurred in 37% of patients for RYBREVANT® and 30% for LAZCLUZE™, rash leading to dose reductions occurred in 23% of patients for RYBREVANT® and 19% for LAZCLUZE™, and rash leading to permanent discontinuation occurred in 5% of patients for RYBREVANT® and 1.7% for LAZCLUZE™.

Indications and Important Safety Information (cont'd)

RYBREVANT® with Carboplatin and Pemetrexed

Based on the pooled safety population, rash occurred in 82% of patients treated with RYBREVANT® in combination with carboplatin and pemetrexed, including Grade 3 (15%) adverse reactions. Rash leading to dose reductions occurred in 14% of patients, and 2.5% permanently discontinued RYBREVANT® and 3.1% discontinued pemetrexed.

RYBREVANT® as a Single Agent

In CHRYSALIS, rash occurred in 74% of patients treated with RYBREVANT® as a single agent, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT® was permanently discontinued due to rash in 0.7% of patients.

Toxic epidermal necrolysis occurred in one patient (0.3%) treated with RYBREVANT® as a single agent.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT® or LAZCLUZE™ in combination with RYBREVANT®. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free (e.g., isopropanol-free, ethanol-free) emollient cream is recommended for dry skin.

When initiating RYBREVANT® treatment with or without LAZCLUZE™, administer alcohol-free emollient cream to reduce the risk of dermatologic adverse reactions. Consider prophylactic measures (e.g. use of oral antibiotics) to reduce the risk of dermatologic reactions. If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. For patients receiving RYBREVANT® in combination with LAZCLUZE™, withhold, reduce the dose, or permanently discontinue both drugs based on severity. For patients receiving RYBREVANT® as a single agent or in combination with carboplatin and pemetrexed, withhold, dose reduce or permanently discontinue RYBREVANT® based on severity.

Ocular Toxicity

RYBREVANT® can cause ocular toxicity including keratitis, blepharitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, eye pruritus, and uveitis.

RYBREVANT® with LAZCLUZE™

In MARIPOSA, ocular toxicity occurred in 16% of patients treated with RYBREVANT® in combination with LAZCLUZE™, including Grade 3 or 4 ocular toxicity in 0.7% of patients. Withhold, reduce the dose, or permanently discontinue RYBREVANT® and continue LAZCLUZE™ based on severity.

Indications and Important Safety Information (cont'd)

RYBREVANT® with Carboplatin and Pemetrexed

Based on the pooled safety population, ocular toxicity occurred in 16% of patients treated with RYBREVANT® in combination with carboplatin and pemetrexed. All events were Grade 1 or 2.

RYBREVANT® as a Single Agent

In CHRYSALIS, keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBREVANT®. All events were Grade 1-2.

Promptly refer patients with new or worsening eye symptoms to an ophthalmologist. Withhold, reduce the dose, or permanently discontinue RYBREVANT® based on severity.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal models, RYBREVANT® and LAZCLUZE™ can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential of the potential risk to the fetus.

Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of RYBREVANT®.

Advise females of reproductive potential to use effective contraception during treatment with LAZCLUZE™ and for 3 weeks after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with LAZCLUZE™ and for 3 weeks after the last dose.

Adverse Reactions

RYBREVANT® with LAZCLUZE™

For the 421 patients in the MARIPOSA clinical trial who received RYBREVANT® in combination with LAZCLUZE™, the most common adverse reactions (≥20%) were rash (86%), nail toxicity (71%), infusion-related reactions (RYBREVANT®, 63%), musculoskeletal pain (47%), stomatitis (43%), edema (43%), VTE (36%), paresthesia (35%), fatigue (32%), diarrhea (31%), constipation (29%), COVID-19 (26%), hemorrhage (25%), dry skin (25%), decreased appetite (24%), pruritus (24%), nausea (21%), and ocular toxicity (16%).

The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased albumin (8%), decreased sodium (7%), increased ALT (7%), decreased potassium (5%), decreased hemoglobin (3.8%), increased AST (3.8%), increased GGT (2.6%), and increased magnesium (2.6%).

Indications and Important Safety Information (cont'd)

Serious adverse reactions occurred in 49% of patients who received RYBREVANT® in combination with LAZCLUZE™. Serious adverse reactions occurring in ≥2% of patients included VTE (11%), pneumonia (4%), ILD/pneumonitis and rash (2.9% each), COVID-19 (2.4%), and pleural effusion and infusion-related reaction (RYBREVANT®) (2.1% each). Fatal adverse reactions occurred in 7% of patients who received RYBREVANT® in combination with LAZCLUZE™ due to death not otherwise specified (1.2%); sepsis and respiratory failure (1% each); pneumonia, myocardial infarction, and sudden death (0.7% each); cerebral infarction, pulmonary embolism (PE), and COVID-19 infection (0.5% each); and ILD/pneumonitis, acute respiratory distress syndrome (ARDS), and cardiopulmonary arrest (0.2% each).

RYBREVANT® with Carboplatin and Pemetrexed

For the 130 patients in the MARIPOSA-2 clinical trial who received RYBREVANT® in combination with carboplatin and pemetrexed, the most common adverse reactions (≥20%) were rash (72%), infusion-related reactions (59%), fatigue (51%), nail toxicity (45%), nausea (45%), constipation (39%), edema (36%), stomatitis (35%), decreased appetite (31%), musculoskeletal pain (30%), vomiting (25%), and COVID-19 (21%). The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased neutrophils (49%), decreased white blood cells (42%), decreased lymphocytes (28%), decreased platelets (17%), decreased hemoglobin (12%), decreased potassium (11%), decreased sodium (11%), increased alanine aminotransferase (3.9%), decreased albumin (3.8%), and increased gamma-glutamyl transferase (3.1%).

In MARIPOSA-2, serious adverse reactions occurred in 32% of patients who received RYBREVANT® in combination with carboplatin and pemetrexed. Serious adverse reactions in >2% of patients included dyspnea (3.1%), thrombocytopenia (3.1%), sepsis (2.3%), and pulmonary embolism (2.3%). Fatal adverse reactions occurred in 2.3% of patients who received RYBREVANT® in combination with carboplatin and pemetrexed; these included respiratory failure, sepsis, and ventricular fibrillation (0.8% each).

For the 151 patients in the PAPILLON clinical trial who received RYBREVANT® in combination with carboplatin and pemetrexed, the most common adverse reactions (≥20%) were rash (90%), nail toxicity (62%), stomatitis (43%), infusion-related reaction (42%), fatigue (42%), edema (40%), constipation (40%), decreased appetite (36%), nausea (36%), COVID-19 (24%), diarrhea (21%), and vomiting (21%). The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased albumin (7%), increased alanine aminotransferase (4%), increased gamma-glutamyl transferase (4%), decreased sodium (7%), decreased potassium (11%), decreased magnesium (2%), and decreases in white blood cells (17%), hemoglobin (11%), neutrophils (36%), platelets (10%), and lymphocytes (11%).

In PAPILLON, serious adverse reactions occurred in 37% of patients who received RYBREVANT® in combination with carboplatin and pemetrexed.

Serious adverse reactions in ≥2% of patients included rash, pneumonia, ILD, pulmonary embolism, vomiting, and COVID-19. Fatal adverse reactions occurred in 7 patients (4.6%) due to pneumonia, cerebrovascular accident, cardio-respiratory arrest, COVID-19, sepsis, and death not otherwise specified.

Indications and Important Safety Information (cont'd)

RYBREVANT® as a Single Agent

For the 129 patients in the CHRYSALIS clinical trial who received RYBREVANT® as a single agent, the most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%). The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%).

Serious adverse reactions occurred in 30% of patients who received RYBREVANT®. Serious adverse reactions in ≥2% of patients included pulmonary embolism, pneumonitis/ILD, dyspnea, musculoskeletal pain, pneumonia, and muscular weakness. Fatal adverse reactions occurred in 2 patients (1.5%) due to pneumonia and 1 patient (0.8%) due to sudden death.

LAZCLUZE™ Drug Interactions

Avoid concomitant use of LAZCLUZE™ with strong and moderate CYP3A4 inducers. Consider an alternate concomitant medication with no potential to induce CYP3A4.

Monitor for adverse reactions associated with a CYP3A4 or BCRP substrate where minimal concentration changes may lead to serious adverse reactions, as recommended in the approved product labeling for the CYP3A4 or BCRP substrate.

Please read full Prescribing Information for RYBREVANT®.
Please read full Prescribing Information for LAZCLUZE™.

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